

Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Online supplementary appendix to:

Molnupiravir for oral treatment of Covid-19 in non-hospitalized patients

Table of Contents

Table S1: List of investigators who randomized at least one participant, by country	2
Table S2: Baseline demographics and clinical characteristics: interim analysis sample	10
Table S3: Baseline demographics and clinical characteristics: all-randomized sample	14
Table S4: Representativeness of trial participants	19
Table S5: Changes in WHO Clinical Progression Scale (all-randomized MITT population)	21
Table S6: Mean change from baseline over time in SARS-CoV-2 nasopharyngeal RNA titer (all-randomized MITT population).....	23
Figure S1: Randomization and flow of participants from baseline through day 29 at the planned interim analysis.....	24
Figure S2: Covid-19 – related hospitalizations or deaths through day 29 (all-randomized MITT population).....	25
Figure S3: Incidence of hospitalization or death by subgroup at day 29 (all-randomized MITT population)	26
Figure S4: Hazard ratio of time to sustained improvement or resolution of self-reported Covid-19 signs/symptoms through day 29 (all-randomized MITT population)	28
Figure S5: Hazard ratio of time to progression of self-reported Covid-19 signs/symptoms through day 29 (all-randomized MITT population).....	29
Figure S6: Longitudinal analysis of mean change from baseline over time in SARS-CoV-2 nasopharyngeal RNA titer (all-randomized MITT population)	30
References.....	31

Table S1: List of investigators who randomized at least one participant, by country

Principal Investigator	Institution, City
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Table S2: Baseline demographics and clinical characteristics: interim analysis sample

	Molnupiravir	Placebo	Total
Participants in population	N=387	N=388	N=775
Sex			
Female, no. (%)	200 (51.7)	171 (44.1)	371 (47.9)
Male, no. (%)	187 (48.3)	217 (55.9)	404 (52.1)
Age (years)			
≤60, no. (%)	336 (86.8)	333 (85.8)	669 (86.3)
>60, no. (%)	51 (13.2)	55 (14.2)	106 (13.7)
Mean (SD)	43.2 (13.5)	44.2 (14.3)	43.7 (13.9)
Median (range)	41.0 (18, 87)	43.0 (18, 88)	41.0 (18, 88)
Race			
American Indian/Alaska Native, no. (%)	20 (5.2)	9 (2.3)	29 (3.7)
Asian, no. (%)	7 (1.8)	11 (2.8)	18 (2.3)
Black/African American, no. (%)	27 (7.0)	20 (5.2)	47 (6.1)
White, no. (%)	194 (50.1)	209 (53.9)	403 (52.0)
Multiple, no. (%)	139 (35.9)	139 (35.8)	278 (35.9)
Ethnicity			
Hispanic Or Latino, no. (%)	224 (57.9)	228 (58.8)	452 (58.3)
Not Hispanic Or Latino, no. (%)	163 (42.1)	159 (41.0)	322 (41.5)

Region						
North America, no. (%)	15	(3.9)	22	(5.7)	37	(4.8)
Latin America, no. (%)	216	(55.8)	214	(55.2)	430	(55.5)
Europe, no. (%)	89	(23.0)	90	(23.2)	179	(23.1)
Asia Pacific, no. (%)	5	(1.3)	6	(1.5)	11	(1.4)
Africa, no. (%)	62	(16.0)	56	(14.4)	118	(15.2)
Risk factors for severe illness from Covid-19						
At least one risk factor, no. (%)	385	(99.5)	384	(99.0)	769	(99.2)
Obesity (BMI ≥30 kg/m ²), no. (%)	306	(79.1)	287	(74.0)	593	(76.5)
Age >60 years, no. (%)	51	(13.2)	55	(14.2)	106	(13.7)
Diabetes mellitus, no. (%)	48	(12.4)	57	(14.7)	105	(13.5)
Serious heart condition, ^a no. (%)	42	(10.9)	36	(9.3)	78	(10.1)
Chronic kidney disease, ^b no. (%)	14	(3.6)	20	(5.2)	34	(4.4)
COPD, no. (%)	7	(1.8)	22	(5.7)	29	(3.7)
Active cancer, ^c no. (%)	6	(1.6)	11	(2.8)	17	(2.2)
Baseline Covid-19 severity						
Mild, no. (%)	222	(57.4)	212	(54.6)	434	(56.0)
Moderate, ^d no. (%)	162	(41.9)	174	(44.8)	336	(43.4)
Severe or Unknown, ^e no. (%)	3	(0.8)	2	(0.5)	5	(0.6)
Baseline clade designation (variant)						
19B	1	(0.3)	1	(0.3)	2	(0.3)

20A	3	(0.8)	2	(0.5)	5	(0.6)
20B	4	(1.0)	4	(1.0)	8	(1.0)
20D	2	(0.5)	1	(0.3)	3	(0.4)
20H (Beta)	5	(1.3)	6	(1.5)	11	(1.4)
20I (Alpha)	12	(3.1)	9	(2.3)	21	(2.7)
20J (Gamma)	35	(9)	48	(12.4)	83	(10.7)
21A, 21I, 21J (Delta)	136	(35.1)	128	(33.0)	264	(34.1)
21G (Lambda)	13	(3.4)	7	(1.8)	20	(2.6)
21H (Mu)	70	(18.1)	81	(20.8)	151	(19.5)
Other, ^f no. (%)	3	(0.8)	3	(0.8)	6	(0.8)
Sequence data not yet available	103	(26.6)	98	(25.3)	201	(25.9)
Time from Covid-19 sign/symptom onset to randomization^g						
≤3 days, no. (%)	191	(49.4)	190	(49.0)	381	(49.2)
>3 days, no. (%)	196	(50.6)	198	(51.0)	394	(50.8)
SARS-CoV-2 RNA at baseline in nasopharyngeal sample (qualitative assay)						
Detectable, no. (%)	332	(85.8)	331	(85.3)	663	(85.5)
Undetectable, no. (%)	28	(7.2)	29	(7.5)	57	(7.4)
Unknown, ^e no. (%)	27	(7.0)	28	(7.2)	55	(7.1)
SARS-CoV-2 baseline viral load in nasopharyngeal sample (quantitative assay)^h						
Detectable (high VL), no. (%)	228	(58.9)	229	(59.0)	457	(59.0)
Detectable (low VL), no. (%)	87	(22.5)	77	(19.8)	164	(21.2)
Undetectable, no. (%)	38	(9.8)	47	(12.1)	85	(11.0)

Unknown, ^e no. (%)	34 (8.8)	35 (9.0)	69 (8.9)
Baseline SARS-CoV-2 nucleocapsid antibody			
Positive, no. (%)	71 (18.3)	70 (18.0)	141 (18.2)
Negative, no. (%)	299 (77.3)	288 (74.2)	587 (75.7)
Unknown, ^e no. (%)	17 (4.4)	30 (7.7)	47 (6.1)

^aSerious heart conditions were defined as heart failure, coronary artery disease, or cardiomyopathies.

^bA diagnosis of chronic kidney disease but excluding patients on dialysis and those with an estimated glomerular filtration rate of less than 30 mL/min/1.73 m² by the MDRD equation, who were not eligible for participation in the trial.

^cActive cancer was defined to exclude minor cancers not associated with immunosuppression or significant morbidity/mortality (e.g., basal cell carcinomas).

^dModerate Covid-19 was defined as (1) shortness of breath with exertion, respiratory rate ≥ 20 to < 30 breaths per min, and/or heart rate ≥ 90 to < 125 beats per minute AND (2) SpO₂ $> 93\%$ on room air or on supplemental oxygen (which has not increased since onset of Covid-19 signs/symptoms) for a reason other than Covid-19 (or patient was receiving ≤ 4 liters/min supplemental oxygen for Covid-19, regardless of SpO₂, but was not previously on supplemental oxygen) AND (3) no shortness of breath at rest, respiratory failure, shock, or multi-organ dysfunction/failure.

^eMissing data, invalid sample, tests not done, or results reported as "unknown" are categorized as unknown.

^fIncludes the following clades: 20C and clade unknown/could not be classified.

^gBased on data collected to stratify at randomization.

^hHigh viral load was defined as $> 10^6$ copies/mL, low viral load was defined as $\leq 10^6$ copies/mL, and undetectable viral load was defined as < 500 copies/mL.

Table S3: Baseline demographics and clinical characteristics: all-randomized sample

	Molnupiravir	Placebo	Total
Participants in population	N=716	N=717	N=1433
Sex			
Female, no. (%)	384 (53.6)	351 (49.0)	735 (51.3)
Male, no. (%)	332 (46.4)	366 (51.0)	698 (48.7)
Age (years)			
≤60, no. (%)	597 (83.4)	590 (82.3)	1187 (82.8)
>60, no. (%)	119 (16.6)	127 (17.7)	246 (17.2)
Mean (SD)	44.4 (14.6)	45.3 (15.0)	44.8 (14.8)
Median (range)	42.0 (18, 90)	44.0 (18, 88)	43.0 (18, 90)
Race			
American Indian/Alaska Native, no. (%)	60 (8.4)	44 (6.1)	104 (7.3)
Asian, no. (%)	26 (3.6)	23 (3.2)	49 (3.4)
Black/African American, no. (%)	40 (5.6)	35 (4.9)	75 (5.2)
White, no. (%)	400 (55.9)	413 (57.6)	813 (56.7)
American Indian/Alaska Native and Black/African American, no. (%)	28 (3.9)	25 (3.5)	53 (3.7)
American Indian/Alaska Native and White, no. (%)	69 (9.6)	88 (12.3)	157 (11.0)

American Indian/Alaska Native, Black/African American, and White, no. (%)	51 (7.1)	46 (6.4)	97 (6.8)
Black/African American and White, no. (%)	41 (5.7)	40 (5.6)	81 (5.7)
Other mixed race, no. (%)	1 (0.1)	3 (0.4)	4 (0.3)
Ethnicity			
Hispanic Or Latino, no. (%)	355 (49.6)	356 (49.7)	711 (49.6)
Not Hispanic Or Latino, no. (%)	355 (49.6)	358 (49.9)	713 (49.8)
Not reported, no. (%)	4 (0.6)	1 (0.1)	5 (0.3)
Unknown, no. (%)	2 (0.3)	2 (0.3)	4 (0.3)
Region			
North America, no. (%)	45 (6.3)	46 (6.4)	91 (6.4)
Latin America, no. (%)	331 (46.2)	330 (46.0)	661 (46.1)
Europe, no. (%)	230 (32.1)	239 (33.3)	469 (32.7)
Asia Pacific, no. (%)	20 (2.8)	17 (2.4)	37 (2.6)
Africa, no. (%)	90 (12.6)	85 (11.9)	175 (12.2)
Risk factors for severe illness from Covid-19			
At least one risk factor, no. (%)	712 (99.4)	712 (99.3)	1424 (99.4)
Obesity (BMI ≥ 30 kg/m ²), no. (%)	538 (75.1)	518 (72.2)	1056 (73.7)
Age >60 years, no. (%)	119 (16.6)	127 (17.7)	246 (17.2)
Diabetes mellitus, no. (%)	107 (14.9)	121 (16.9)	228 (15.9)
Serious heart condition, ^a no. (%)	86 (12.0)	81 (11.3)	167 (11.7)
Chronic kidney disease, ^b no. (%)	38 (5.3)	46 (6.4)	84 (5.9)

COPD, no. (%)	22	(3.1)	35	(4.9)	57	(4.0)
Active cancer, ^c no. (%)	13	(1.8)	16	(2.2)	29	(2.0)
Baseline Covid-19 severity						
Mild, no. (%)	395	(55.2)	390	(54.4)	785	(54.8)
Moderate, ^d no. (%)	315	(44.0)	323	(45.0)	638	(44.5)
Severe, no. (%)	3	(0.4)	1	(0.1)	4	(0.3)
Unknown, ^e no. (%)	3	(0.4)	3	(0.4)	6	(0.4)
Baseline clade designation (variant)						
19B	3	(0.4)	3	(0.4)	6	(0.4)
20A	4	(0.6)	3	(0.4)	7	(0.5)
20B	4	(0.6)	4	(0.6)	8	(0.6)
20D	2	(0.3)	3	(0.4)	5	(0.3)
20H (Beta)	5	(0.7)	6	(0.8)	11	(0.8)
20I (Alpha)	12	(1.7)	9	(1.3)	21	(1.5)
20J (Gamma)	37	(5.2)	48	(6.7)	85	(5.9)
21G (Lambda)	14	(2.0)	7	(1.0)	21	(1.5)
21H (Mu)	76	(10.6)	86	(12.0)	162	(11.3)
21A, 21I, 21J (Delta)	237	(33.1)	223	(31.1)	460	(32.1)
Other, ^f no. (%)	3	(0.4)	3	(0.4)	6	(0.4)
Sequence data not yet available	319	(44.6)	322	(44.9)	641	(44.7)
Time from Covid-19 sign/symptom onset to randomization^g						
≤3 days, no. (%)	342	(47.8)	342	(47.7)	684	(47.7)

>3 days, no. (%)	374 (52.2)	375 (52.3)	749 (52.3)
SARS-CoV-2 baseline viral load in nasopharyngeal sample (quantitative assay)^h			
Detectable (high VL), no. (%)	389 (54.3)	383 (53.4)	772 (53.9)
Detectable (low VL), no. (%)	161 (22.5)	163 (22.7)	324 (22.6)
Undetectable, no. (%)	64 (8.9)	71 (9.9)	135 (9.4)
Unknown, ^e no. (%)	102 (14.2)	100 (13.9)	202 (14.1)
SARS-CoV-2 RNA at baseline in nasopharyngeal sample (qualitative assay)			
Detectable, no. (%)	615 (85.9)	615 (85.8)	1230 (85.8)
Undetectable, no. (%)	54 (7.5)	51 (7.1)	105 (7.3)
Unknown, ^e no. (%)	47 (6.6)	51 (7.1)	98 (6.8)
Baseline SARS-CoV-2 nucleocapsid antibody			
Positive, no. (%)	137 (19.1)	147 (20.5)	284 (19.8)
Negative, no. (%)	541 (75.6)	521 (72.7)	1062 (74.1)
Unknown, ^e no. (%)	38 (5.3)	49 (6.8)	87 (6.1)

^aSerious heart conditions were defined as heart failure, coronary artery disease, or cardiomyopathies.

^bA diagnosis of chronic kidney disease but excluding patients on dialysis and those with an estimated glomerular filtration rate of less than 30 mL/min/1.73 m² by the MDRD equation, who were not eligible for participation in the trial.

^cActive cancer was defined to exclude minor cancers not associated with immunosuppression or significant morbidity/mortality (e.g., basal cell carcinomas).

^dModerate Covid-19 was defined as (1) shortness of breath with exertion, respiratory rate ≥ 20 to < 30 breaths per min, and/or heart rate ≥ 90 to < 125 beats per minute AND (2) SpO₂ $> 93\%$ on room air or on supplemental oxygen (which has not increased since onset of Covid-19 signs/symptoms) for a reason other than Covid-19 (or patient was receiving ≤ 4 liters/min supplemental oxygen for Covid-19, regardless of SpO₂, but was not previously on supplemental oxygen) AND (3) no shortness of breath at rest, respiratory failure, shock, or multi-organ dysfunction/failure.

^eMissing data, invalid sample, tests not done, or results reported as "unknown" are categorized as unknown.

^fIncludes the following clades: 20C and clade unknown/could not be classified.

^gBased on data collected to stratify at randomization.

^bHigh viral load was defined as $>10^6$ copies/mL, low viral load was defined as $\leq 10^6$ copies/mL, and undetectable viral load was defined as <500 copies/mL.

Table S4: Representativeness of trial participants

Disease under investigation	Covid-19.
Special considerations related to	
Sex and gender	Covid-19 affects men and women with equal frequency, however severe Covid-19 (i.e., disease requiring hospitalization) appears to be somewhat more frequent in men, ^{1,2} and hospitalization and/or death were the primary endpoint of this trial. Gender identity is not known to impact either case, fatality, or hospitalization rates with this disease, but this is a topic of active research. ¹
Age	Data from the CDC show that Covid-19 case rates are similar across all age groups, other than children younger than 4 years old (excluded from this trial conducted in adults). Older age is a well-established risk factor for severe Covid-19, with hospitalization and mortality rates increasing substantially in patients older than 50 years. Compared with 18–29-year-old patients, the risk for hospitalization is 4 times higher in 50–64-year-old patients and 15 times higher in patients 85 years and older. The mortality risk is 30 times and 570 times higher, respectively. ³
Race or ethnic group	Covid-19 affects Black/African American, Hispanic/Latino, and American Indian/Alaska Native persons disproportionately in the United States, both in terms of case rates and the incidence of severe disease. In these groups, the hospitalization risk is ~3 times and the mortality risk ~2 times as high as in non-Hispanic White persons. In comparison, non-Hispanic Asian persons have a slightly lower case and similar hospitalization/mortality rates as non-Hispanic White persons. ⁴
Geography	The Covid-19 pandemic is a global problem not limited to any specific country or region. Incidence and mortality rates vary greatly within and between countries, depending on a complex interplay of factors including, but not limited to healthcare infrastructure, access to healthcare (which can be affected by Covid-19 surges/waves), prevalence of risk factors (e.g., national obesity rates), average population age, vaccination rates, and circulating variants.
Other considerations	Besides age, race, and ethnicity, there are a number of well-established risk factors for hospitalization and/or death from Covid-19, including obesity, diabetes mellitus, serious heart conditions, active cancer, chronic kidney disease, and chronic obstructive pulmonary disease. ⁵
Overall representativeness of this trial	By design, trial participants were limited to those with at least 1 well-established risk factors for severe Covid-19; predominant risk factors in our trial population were obesity (74%), age >60 years (17%), and diabetes mellitus (16%), but all predefined risk factors were well represented. All participants self-reported as not having been vaccinated for Covid-19, another important risk factor for severe disease. Of note, there are other risk factors for developing severe disease from Covid-19 that were not systematically assessed in our trial population (e.g., depression and other mental health disorders, neurologic disorders) but were present at least to some degree in the trial population. Further, other

	<p>known risk factors, e.g., certain types of immuno-suppressed status, were predefined exclusion criteria and thus not represented at all.</p> <p>Participant sex and age were reported by the investigator; due to legal restrictions imposed by some countries in which this study was conducted, we did not ask participants to self-report their gender. Race and ethnicity were self-reported by trial participants. As would be expected from an overall at-risk population, an almost equivalent proportion of participants were male and female. About 34% of participants were 50 years old or older, with 11% of all participants being 65 years old or older. The representativeness of the trial participants' age depends on any one country's individual population age stratification, but participants with age >65 years old appear to be somewhat underrepresented if specifically considering the age distribution of countries such as the United States (where about 16% are >65 years old), member states of the European Union (17%), and Japan (29%).</p> <p>Participants were enrolled worldwide, with most participants from Latin America (46%), Europe (33%), and Africa (12%). Only about 6% of participants came from the United States. Black/African American persons were underrepresented in our trial population (5%); however, 21% of all randomized participants self-identified as both Black and of another race. Hispanic/Latino persons were highly represented in this trial, comprising 50% of the randomized population, in large part reflecting the proportion of patients enrolled in Latin America.</p>
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Table S5: Changes in WHO Clinical Progression Scale (all-randomized MITT population)

The WHO Clinical Progression Scale is an 11-point ordinal scale (ranging from 0 through 10), measuring the clinical progression of Covid-19.⁶ The minimally important difference is not known. Scores are assigned as follows:

Score 0: Uninfected, no SARS-CoV-2 viral RNA detected.

Score 1: Asymptomatic, but SARS-CoV-2 viral RNA detected.

Score 2: Symptomatic, but able to function independently.

Score 3: Symptomatic and assistance needed.

Score 4: Hospitalized, without oxygen therapy. [*Note: Patients hospitalized for observation only were assigned a score of 1, 2, or 3, depending on their symptoms or condition, as per those respective scoring categories.*]

Score 5: Hospitalized and administered oxygen by mask or nasal prongs.

Score 6: Hospitalized and administered oxygen by non-invasive ventilation or high flow.

Score 7: Intubated and receiving mechanical ventilation, $\text{PiO}_2/\text{FiO}_2 \geq 150$ or $\text{SpO}_2/\text{FiO}_2 \geq 200$.

Score 8: Receiving mechanical ventilation $\text{PiO}_2/\text{FiO}_2 < 150$ ($\text{SpO}_2/\text{FiO}_2 < 200$) or vasopressors.

Score 9: Receiving mechanical ventilation $\text{PiO}_2/\text{FiO}_2 < 150$ and vasopressors, dialysis, or extracorporeal membrane oxygenation.

Score 10: Dead.

Visit	Score category	Molnupiravir	Placebo
		N=709 no./m (%)	N=699 no./m (%)
Baseline	0	0/706 (0.0)	0/695 (0.0)
	1-3	706/706 (100.0)	695/695 (100.0)
	4-5	0/706 (0.0)	0/695 (0.0)
	6-9	0/706 (0.0)	0/695 (0.0)
	10	0/706 (0.0)	0/695 (0.0)
	Missing	3	4
Day 3	0	2/695 (0.3)	3/684 (0.4)
	1-3	679/695 (97.7)	663/684 (96.9)
	4-5	11/695 (1.6)	17/684 (2.5)
	6-9	3/695 (0.4)	1/684 (0.1)
	10	0/695 (0.0)	0/684 (0.0)
	Missing	14	15
	Odds ratio (95% CI)	1.19 (0.62, 2.30)	
Day 5	0	11/697 (1.6)	10/684 (1.5)
	1-3	663/697 (95.1)	636/684 (93.0)
	4-5	17/697 (2.4)	34/684 (5.0)
	6-9	6/697 (0.9)	4/684 (0.6)

	10 Missing Odds ratio (95% CI)	0/697 (0.0) 12	0/684 (0.0) 15
		1.52 (0.96, 2.39)	
Day 10	0	40/673 (5.9)	32/673 (4.8)
	1-3	599/673 (89.0)	580/673 (86.2)
	4-5	27/673 (4.0)	44/673 (6.5)
	6-9	7/673 (1.0)	17/673 (2.5)
	10	0/673 (0.0)	0/673 (0.0)
	Missing	36	26
	Odds ratio (95% CI)	1.58 (1.14, 2.20)	
Day 15	0	102/669 (15.2)	94/667 (14.1)
	1-3	548/669 (81.9)	525/667 (78.7)
	4-5	15/669 (2.2)	33/667 (4.9)
	6-9	4/669 (0.6)	10/667 (1.5)
	10	0/669 (0.0)	5/667 (0.7)
	Missing	40	32
	Odds ratio (95% CI)	1.36 (1.03, 1.78)	
Day 29	0	312/645 (48.4)	314/650 (48.3)
	1-3	324/645 (50.2)	314/650 (48.3)
	4-5	6/645 (0.9)	12/650 (1.8)
	6-9	2/645 (0.3)	1/650 (0.2)
	10	1/645 (0.2)	9/650 (1.4)
	Missing	64	49
	Odds ratio (95% CI)	1.04 (0.84, 1.29)	

Odds ratios were estimated using the proportional odds model with WHO 11-point Clinical Progression Score categories as the response variable. Day 3 includes post-baseline records up to day 4 relative to randomization. Day 5 includes post-baseline records from day 5 (relative to randomization) up to day 7. End of treatment visits occurring earlier than day 5 (relative to randomization) are included in the day 3 visit.

CI, confidence interval. m, number of participants with non-missing ordinal scale at the time point assessed. no., number of participants in each subcategory. N, number of participants in each treatment group.

Table S6: Mean change from baseline over time in SARS-CoV-2 nasopharyngeal RNA titer (all-randomized MITT population)

Visit	Molnupiravir			Placebo		
	no.	Mean ^a	Mean change ^a (SD)	no.	Mean ^a	Mean change ^a (SD)
SARS-CoV-2 RNA Titer (log₁₀ copies/ml)						
Baseline	549	6.81	-	544	6.81	-
Day 3	499	5.74	-1.08 (1.287)	507	6.00	-0.84 (1.258)
EOT (Day 5)	482	4.73	-2.09 (1.490)	482	5.04	-1.79 (1.513)
Day 10	447	3.64	-3.18 (1.628)	438	3.80	-2.99 (1.678)
Day 15	424	3.18	-3.61 (1.740)	413	3.28	-3.48 (1.836)
Day 29	373	2.88	-3.91 (1.656)	362	2.88	-3.99 (1.712)
SARS-CoV-2 RNA titer (log₁₀ copies/ml) in participants with baseline RNA titer ≤10⁶ copies/ml						
Baseline	160	4.66	-	162	4.61	-
Day 3	144	3.92	-0.71 (1.249)	146	4.32	-0.28 (1.284)
EOT (Day 5)	140	3.56	-1.05 (1.182)	140	3.67	-0.91 (1.398)
Day 10	128	3.01	-1.62 (1.005)	132	3.18	-1.37 (1.276)
Day 15	125	2.98	-1.61 (1.115)	130	3.14	-1.42 (1.268)
Day 29	108	2.81	-1.77 (0.957)	103	2.79	-1.76 (0.978)
SARS-CoV-2 RNA titer (log₁₀ copies/ml) in participants with baseline RNA titer >10⁶ copies/ml						
Baseline	389	7.69	-	382	7.74	-
Day 3	355	6.48	-1.23 (1.273)	361	6.68	-1.07 (1.175)
EOT (Day 5)	342	5.21	-2.52 (1.393)	342	5.60	-2.15 (1.409)
Day 10	319	3.90	-3.81 (1.394)	306	4.07	-3.70 (1.304)
Day 15	299	3.26	-4.44 (1.184)	283	3.35	-4.42 (1.163)
Day 29	265	2.91	-4.78 (0.924)	259	2.92	-4.88 (0.963)

Analysis only includes participants with baseline nasopharyngeal SARS-CoV-2 RNA titer ≥ 500 copies/mL. The quantitative assay to generate these data was the Q2 SARS-CoV-2 Viral Load Quantitation Assay, with lower limit of quantification of 500 copies/ml and upper limit of quantification of 500,000,000 copies/ml. Post-baseline results below or above these limits were included in the mean and the mean change from baseline, with imputed value 499 and 500,000,001, respectively. Day 3 includes post-baseline records up to day 4. EOT (day 5) includes post-baseline records from day 5 up to day 7. EOT visits occurring earlier than day 5 are included in the day 3 visit.

^aMean and mean change from baseline are based on the measurements from participants with values at both baseline and at the time point assessed.

EOT, end of treatment. no., Number of participants with baseline and at least one postbaseline test result at the time point assessed. SD, Standard deviation.

Figure S1: Randomization and flow of participants from baseline through day 29 at the planned interim analysis

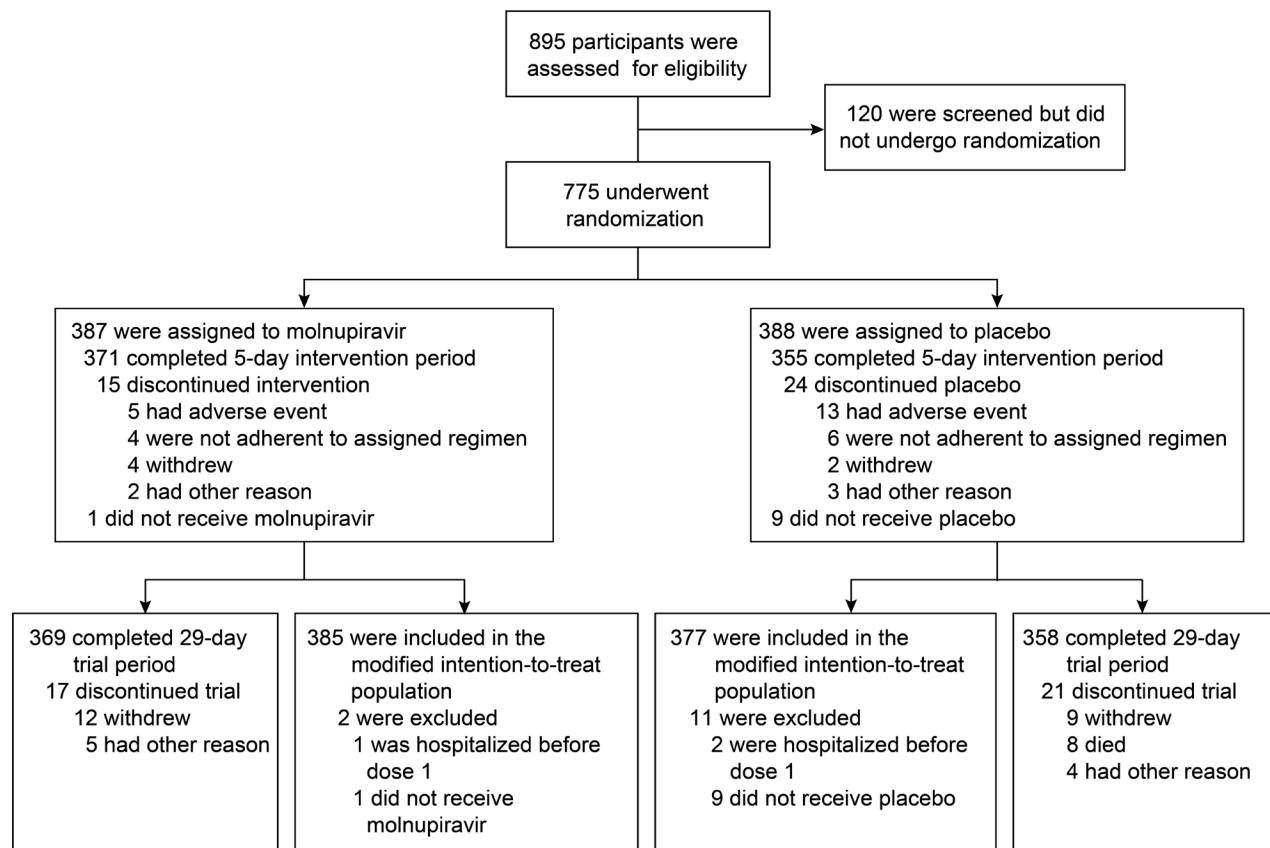
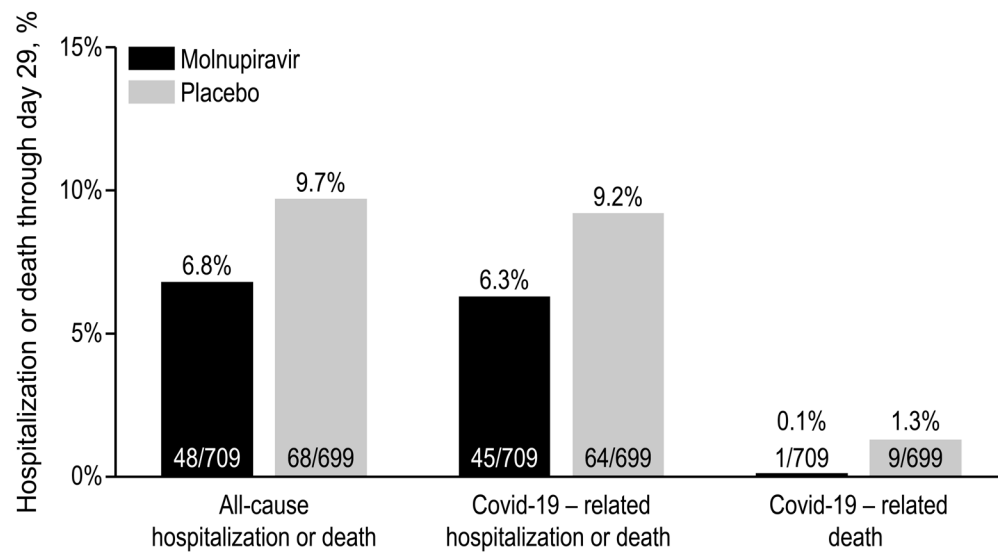
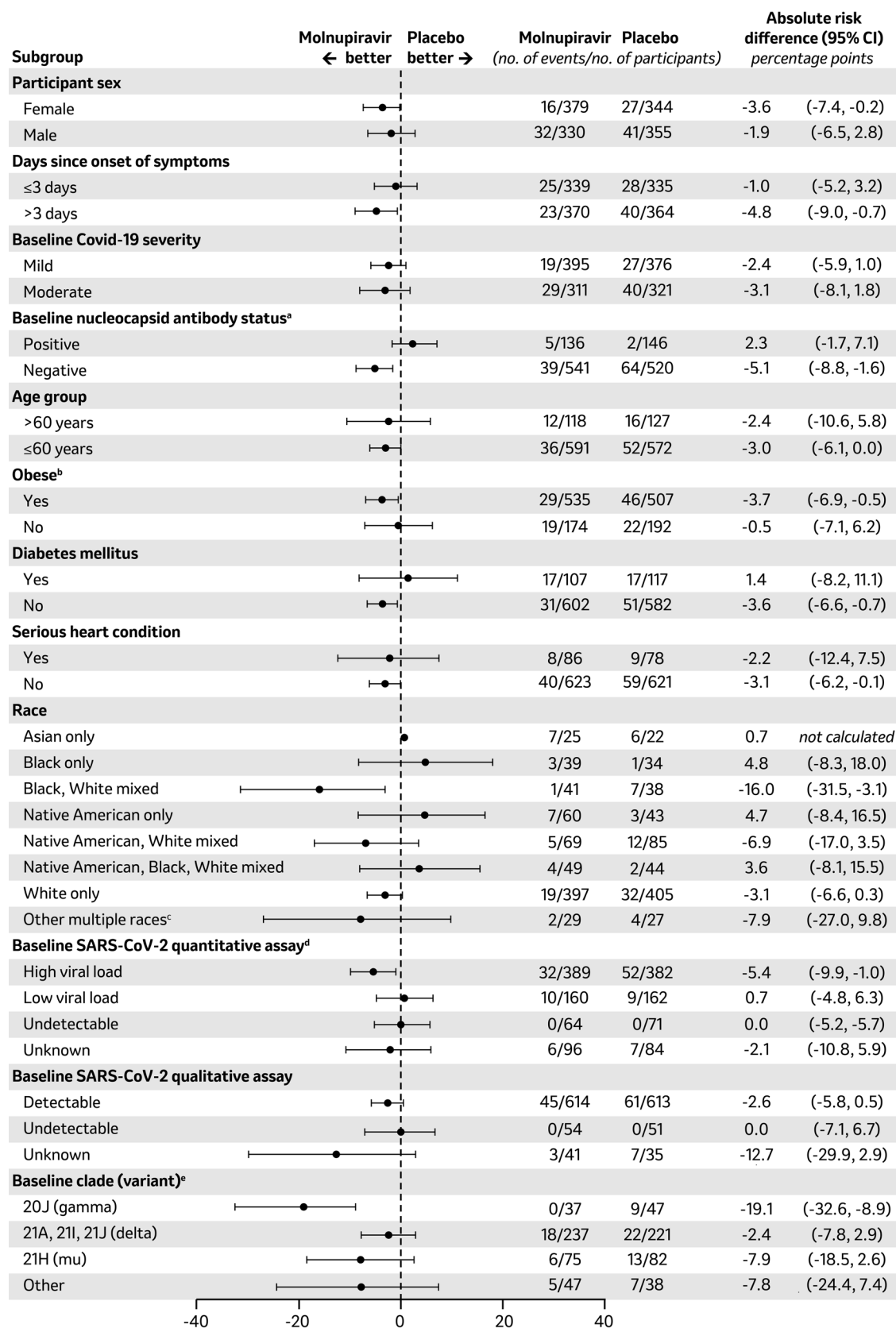


Figure S2: Covid-19 – related hospitalizations or deaths through day 29 (all-randomized MITT population)



For the single participant who died in the molnupiravir group, the cause of death was reported as multiorgan failure with Covid-19 as a contributing factor; this participant was 81 years old, had active, metastatic cancer as an underlying comorbidity, was reported to have bacterial community-acquired pneumonia on day 7, was hospitalized for pneumonia on day 15, and died on day 26.

Figure S3: Incidence of hospitalization or death by subgroup at day 29 (all-randomized MITT population)



At the time of this report, on-going sequencing for baseline clade had not yet been done for 44.7% of all randomized participants; outcomes according to baseline variants are only shown for the 55.7% of all modified intention-to-treat participants whose nasopharyngeal samples had already undergone sequencing. Among participants whose baseline clade sequence is still pending analysis, a heterogeneous sample that does not represent a clinical entity, 19/313 (6.1%) participants receiving molnupiravir and 17/311 (5.5%) receiving placebo were hospitalized or died by day 29.

As per the statistical analysis plan, confidence intervals were not calculated for subgroups with <25 participants in either arm.

^aData are based on nucleocapsid antibody assay and do not reflect prior vaccination status, since Covid-19 vaccines generate antibodies against the SARS-CoV-2 spike protein, not the SARS-CoV-2 nucleocapsid protein.

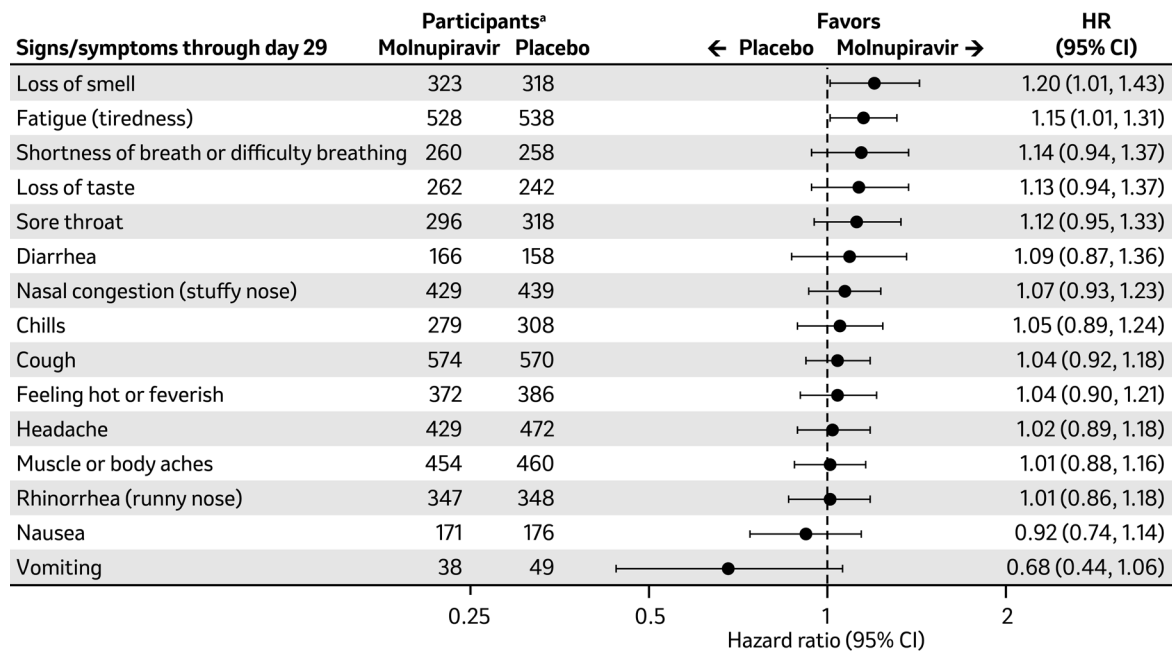
^bObesity was defined by a body-mass index of 30 or above.

^cIncludes participants who self-identified as mixed Asian, Black/African American, and White and participants who self-identified as mixed American Indian/Alaska Native and Black/African American.

^dHigh viral load was defined as $>10^6$ copies/mL, low viral load was defined as $\leq 10^6$ copies/mL, and undetectable viral load was defined as <500 copies/mL.

^eThe final effect estimate is unknown, pending completion of all baseline sequencing; the current effect size may be an over- or under-estimate. “Other” includes the following clades: 19B, 20A, 20B, 20C, 20D, and unknown clades or those that could not be classified.

Figure S4: Hazard ratio of time to sustained improvement or resolution of self-reported Covid-19 signs/symptoms through day 29 (all-randomized MITT population)

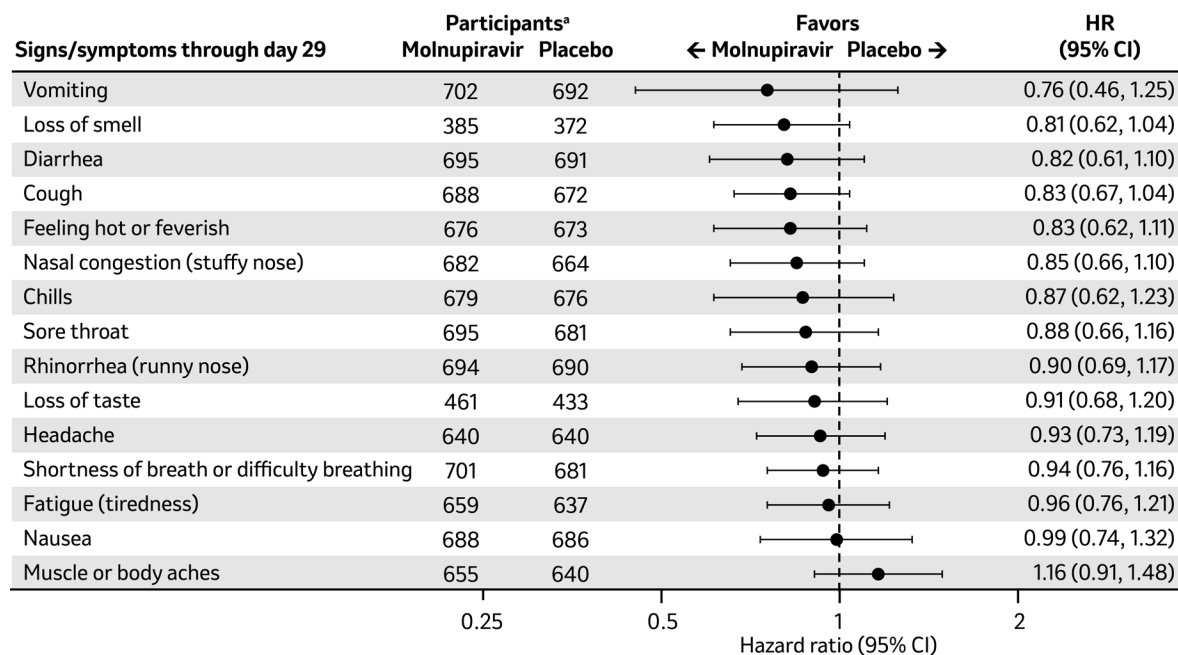


Based on Cox regression model with Efron's method of tie handling with treatment and randomization stratification factor as covariates. Hazard ratio >1 favors the molnupiravir group.

^aNumber of participants eligible for sustained improvement or resolution (i.e., those who had the corresponding sign or symptom at baseline [at any severity]) in the MITT population.

CI, confidence interval. HR, hazard ratio. MITT, modified intention-to-treat population.

Figure S5: Hazard ratio of time to progression of self-reported Covid-19 signs/symptoms through day 29 (all-randomized MITT population)

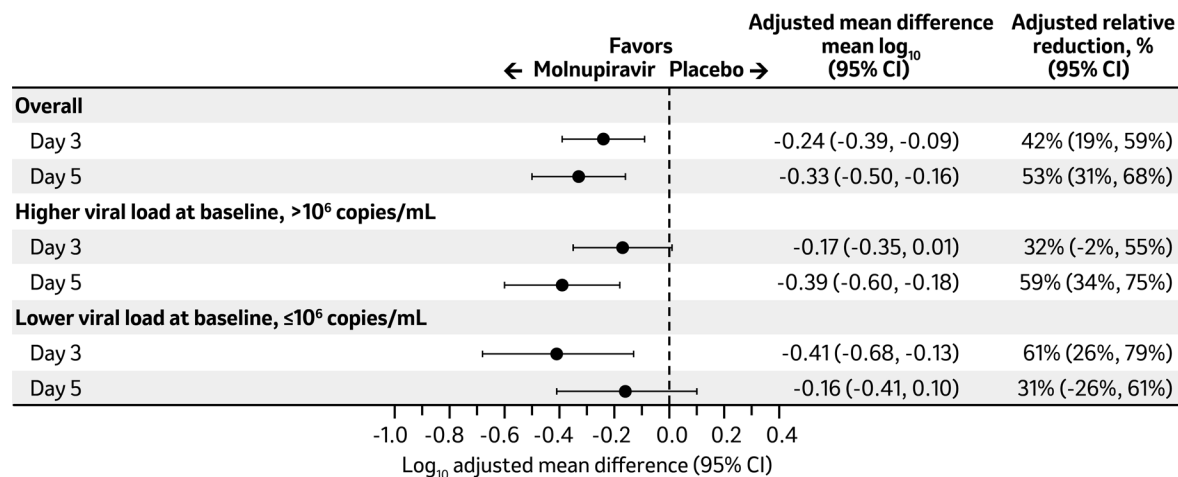


Based on Cox regression model with Efron's method of tie handling with treatment and randomization stratification factor as covariates. Hazard ratio <1 favors the molnupiravir group.

^aNumber of participants at risk for progression (i.e., those without the sign or symptom at baseline or had the sign or symptom at baseline at mild or moderate severity) in the MITT population.

CI, confidence interval. HR, hazard ratio. MITT, modified intention-to-treat population.

Figure S6: Longitudinal analysis of mean change from baseline over time in SARS-CoV-2 nasopharyngeal RNA titer (all-randomized MITT population)



Treatment differences in change in viral load from baseline over time were estimated using the constrained full likelihood longitudinal data analysis (cLDA) model proposed by Liang and Zeger.⁷ The cLDA model included baseline viral load as one of the repeated measures, with a constraint of equal means across randomized groups at baseline due to randomization. The model included terms for intervention group, visit, interaction of intervention group and visit, and the randomization factor of time from sign/symptom onset prior to randomization (≤ 3 days vs > 3 days). The marginal mean difference in responses between intervention groups was then estimated based on the model.

Analysis only included participants with baseline SARS-CoV-2 RNA titer ≥ 500 copies/mL. The quantitative assay to generate these data was the Q2 SARS-CoV-2 Viral Load Quantitation Assay, with lower limit of quantification of 500 copies/ml and upper limit of quantification of 500,000,000 copies/ml. Postbaseline results below or above these limits were included in the mean and mean change from baseline, with imputed value 499 and 500,000,001, respectively. Day 3 includes post-baseline records up to day 4. EOT (day 5) includes post-baseline records from day 5 up to day 7. EOT visits occurring earlier than day 5 are included in the day 3 visit.

CI, confidence interval.

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